

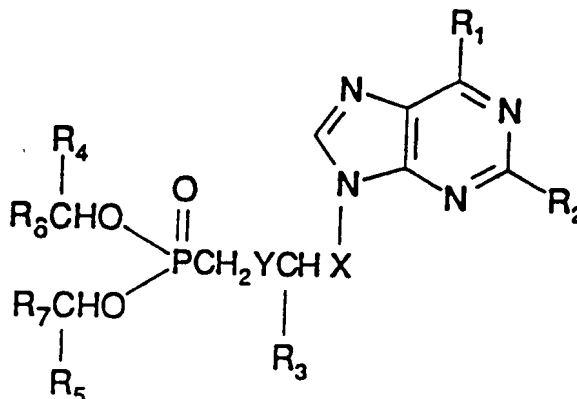


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB91/02113 (22) International Filing Date: 28 November 1991 (28.11.91) (30) Priority data: 9026164.5 1 December 1990 (01.12.90) GB (71) Applicant (for all designated States except US): BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HARNDEN, Michael, Raymond [GB/GB]; BAILEY, Stuart [GB/GB]; SERAFINOWSKA, Halina, Teresa [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).		(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

08/900,746

(54) Title: PHARMACEUTICALS



(I)

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein X is $-\text{CH}_2\text{O}$, $-\text{CH}_2$ or $-\text{CH}(\text{CH}_2\text{OR}_8)\text{O}$ where R_8 is hydrogen or acyl; Y is O or S; R_1 is hydroxy or amino; R_2 is amino or hydrogen; R_3 is hydrogen or, when X is CH_2O and Y is O, R_3 may be CH_2OR_9 where R_9 is hydrogen or acyl; R_4 and R_5 are both hydrogen or the same C_{1-4} alkyl group; and R_6 and R_7 are independently C_{2-7} alkanoyloxy or benzoyloxy wherein the phenyl moiety is optionally substituted.

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PHARMACEUTICALS

5 The present invention relates to novel compounds which are of potential use as antiviral agents, to processes for their preparation and to their use as pharmaceuticals.

EP-A-319228 and EP-A-353955 (Beecham Group p.l.c.) disclose a group of purine derivatives containing a 9-[2-(phosphonomethoxy)alkoxy] substituent, which are described as having antiviral activity.

10

EP-A-206459 (Ceskoslovenska akademie ved) discloses a group of 9-(phosphonomethoxyalkyl)adenines, which are described as having antiviral activity.

15 'Nucleotide Analogues as Antiviral Agents' ACS Symposium Series 401, Editor J.C. Martin, published by the American Chemical Society, Washington DC (1989) Chapters 4 and 5 discloses, a number of (phosphonomethoxyalkyl) derivatives of purines and pyrimidines and their antiviral activity.

20

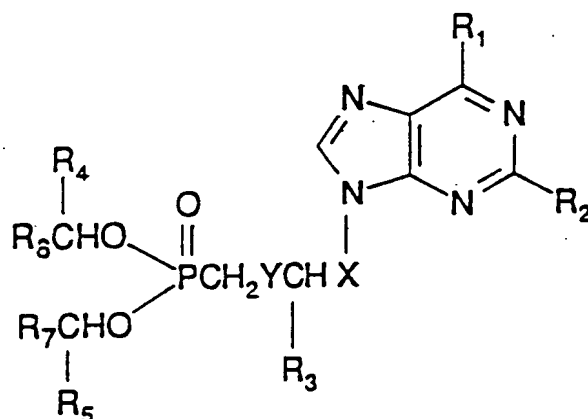
Particular compounds of interest are adenine or guanine having a 9-substituent as follows:

(HO) ₂ POCH ₂ OCH ₂ CH ₂ O-	Ex.1, EP-A-319228
(HO) ₂ POCH ₂ OCH ₂ CH(CH ₂ OH)O-	Ex.16, EP-A-206459
(HO) ₂ POCH ₂ OCH ₂ CH ₂ -	PMEA/PMEG
(HO) ₂ POCH ₂ OCH(CH ₂ OH)CH ₂ -	HPMPA/HPMPG

25 It has now been discovered that certain derivatives of these compounds are prodrugs therefore, having improved gastrointestinal absorption properties.

30 Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

- 2 -



(I)

5 wherein

X is $-\text{CH}_2\text{O}$, $-\text{CH}_2$ or $-\text{CH}(\text{CH}_2\text{OR}_8)\text{O}$ where R_8 is hydrogen or acyl;

Y is O or S;

R_1 is hydroxy or amino;

10 R_2 is amino or hydrogen;

R_3 is hydrogen or, when X is CH_2O and Y is O, R_3 may be CH_2OR_9 where R_9 is hydrogen or acyl;

R_4 and R_5 are both hydrogen or the same C_{1-4} alkyl group; and

15 R_6 and R_7 are independently C_{2-7} alkanoyloxy or benzoyloxy wherein the phenyl moiety is optionally substituted.

When R_1 is hydroxy and R_2 is amino, the compound of formula (I) is a guanine derivative;

20 When R_1 is amino and R_2 is hydrogen, the compound of formula (I) is an adenine derivative;

When R_1 is hydroxy and R_2 is hydrogen, the compound of formula (I) is a hypoxanthine derivative; and

25

When R_1 and R_2 are both amino groups, the compound of formula (I) is a 2,6-diaminopurine derivative.

Often, the compound of formula (I) is a guanine or adenine derivative.

30

- 3 -

Suitable examples of R_4 and R_5 include hydrogen, methyl, ethyl, *n*- and *iso*-propyl, preferably hydrogen or methyl.

5 Suitable examples of R_6 and R_7 when alkanoyloxy include acetoxy, propionyloxy, butanoyloxy, pentanoyloxy and hexanoyloxy, straight chain or branched; in particular pivaloyloxy. R_6 and R_7 when benzoyloxy may be optionally substituted as defined below for R_8/R_9 benzoyl.

10 Suitable examples of R_8/R_9 when, acyl include carboxylic acyl, such as C_{1-7} alkanoyl and benzoyl optionally substituted in the phenyl ring by one, two or three groups or atoms selected from halogen, such as fluoro, chloro, bromo, and C_{1-4} alkyl or C_{1-4} alkoxy wherein the alkyl moiety is selected from methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl. Preferred acyl groups include acetyl, propionyl, butyryl, heptanoyl and
15 hexanoyl.

There are groups of compounds of interest wherein:

- 20 i) X is $-\text{CH}_2\text{O}$ and R_3 is hydrogen.
ii) X is $-\text{CH}_2\text{O}$ and R_3 is CH_2OR_9 as defined.
iii) X is $-\text{CH}_2(\text{CH}_2\text{OR}_8)\text{O}$ as defined and R_3 is hydrogen.
25 iv) X is $-\text{CH}_2$ and R_3 is hydrogen.
v) X is $-\text{CH}_2$ and R_3 is CH_2OR_9 as defined.

30 Y is preferably O.

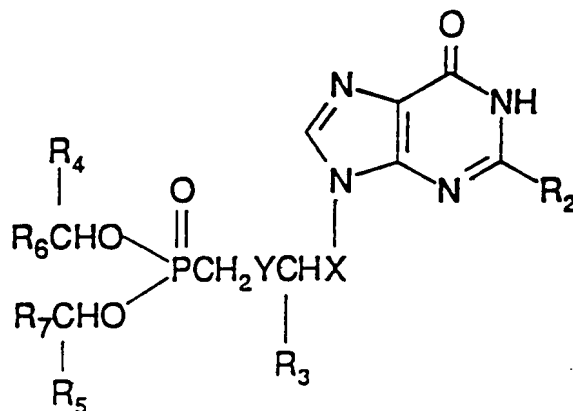
Examples of pharmaceutically acceptable salts of the compound of formula (I) are acid addition salts formed with a pharmaceutically acceptable acid such as hydrochloric acid, orthophosphoric acid and sulphuric acid. Pharmaceutically acceptable salts also include those formed with organic
35 bases, preferably with amines, such as ethanolamines or diamines; and alkali metals, such as sodium and potassium.

It will be appreciated that some of the compounds of formula (I), especially

those wherein $R_3/R_4/R_5$, is other than hydrogen, have an asymmetric centre, and therefore are capable of existing in more than one stereoisomeric form. The invention extends to each of these forms individually and to mixtures thereof, including racemates. The isomers
 5 may be separated conventionally by chromatographic methods or using a resolving agent. Alternatively, the individual isomers may be prepared by asymmetric synthesis using chiral intermediates.

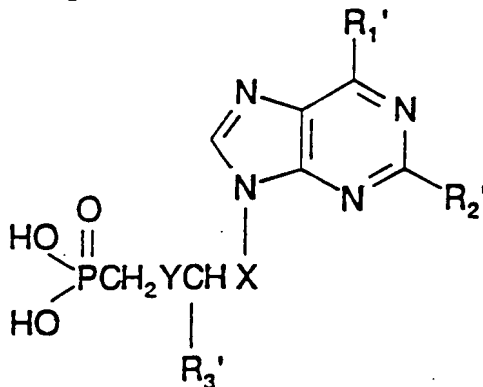
The compounds of formula (I) including their alkali metal salts may form
 10 solvates such as hydrates and these are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will be appreciated that, when R_1 is hydroxy in formula (I) the compound exists in the predominant tautomeric form of structure (IA):
 15



(IA)

The invention also provides a process for the preparation of a compound of
 20 formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with R_6R_4CHQ and R_7R_5CHQ wherein Q is a leaving group and R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are as defined in formula (I), and thereafter optionally forming a pharmaceutically acceptable salt thereof.

- 5 The compound of formula (II) is preferably in the form of a suitable salt, such as the tetrabutylammonium salt, the tetramethylammonium salt and those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)amine. The triethylamine salt is preferred.

10

Suitable values for Q include halo, such as chloro.

15

The reaction takes place in a suitable inert solvent such as N,N-dimethylformamide (DMF) OR 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU), at elevated temperatures 20-100°C, preferably 30-80°C.

20

Suitable examples of protecting groups and their removal, are as described in EP-A-242482. A particularly suitable protecting group is the t-butyldiphenylsilyl group removable by conventional methods.

25

It will be appreciated that the above conversions may take place in any desired or necessary order, having regard to the final desired compound of formula (I).

Compounds of the formula (II) are prepared as described in EP-A-313289 and the aforementioned publications, the subject matter of which are incorporated herein by reference.

30

When R_8/R_9 is hydroxy, appropriate selective protection may be required, eg using acetate.

35

Pharmaceutically acceptable salts may be prepared in conventional manner, for example, in the case of acid addition salts, by reaction with the appropriate organic or inorganic acid.

It will be appreciated that the invention provides a process for the preparation of a compound of formula (I) wherein R_8/R_9 is hydrogen which process comprises the deprotection of a corresponding compound of

formula (I) wherein Rg/Rg is protected hydroxy.

Preferred methods for deprotection, as hereinbefore described, include removal of the acetyl group.

5

The compounds of the invention are of potential use in the treatment of infections caused by viruses, in particular DNA viruses and retroviruses. Examples of DNA viruses include herpesviruses such as herpes simplex types 1 and 2, varicella-zoster virus, Epstein-Barr virus and
10 cytomegalovirus. Examples of retroviruses include lentiviruses such as visna virus and human immunodeficiency virus (strains 1 and 2).

The compounds may also be inhibitors of tumorigenic viruses and/or of potential use in the treatment of neoplastic diseases, i.e. cancer.

15

Compounds of the invention may be formulated for use in a pharmaceutical composition. Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of formula (I) or pharmaceutically acceptable salt
20 thereof together with a pharmaceutically acceptable carrier or excipient.

A composition which may be administered by the oral route to humans may be compounded in the form of a syrup, tablet or capsule. When the composition is in the form of a tablet, any pharmaceutical carrier suitable
25 for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose, glucose, rice, flour and chalk. The composition may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl
30 alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups. The compounds may also be presented with a sterile liquid carrier for injection.

The composition may also be formulated for topical application to the skin
35 or eyes.

For topical application to the skin, the composition may be in the form of a cream, lotion or ointment. These formulations may be conventional

formulations well known in the art, for example, as described in standard books of pharmaceuticals and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books and the British Pharmacopoeia.

- 5 The composition for application to the eyes may be a conventional eye-drop composition well known in the art, or an ointment composition.

Preferably, the composition of this invention is in unit dosage form or in some other form that may be administered in a single dose. A suitable
10 dosage unit might contain from 50 mg to 1 g of active ingredient, for example 100 to 500 mg.

Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound will in general be in the
15 range of from 1.0 to 20 mg/kg of body weight per day or more usually 2.0 to 10 mg/kg per day.

No unacceptable toxicological effects are indicated at the above described dosage levels.

20 The invention also provides a method of treating viral infections in a human or non-human animal, which comprises administering to the animal an effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

25 The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for the treatment of viral infections.

30 The compounds of the invention are also believed to exhibit a synergistic antiviral effect in conjunction with interferons; and combination products comprising these two components for sequential or concomitant administration, by the same or different routes, are therefore within the ambit of the present invention.

35 The following examples illustrate the invention.

Examples

The following compounds of formula (I) were prepared:

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆ /R ₇	X	Y
NH ₂	H	H	H	H	(CH ₃) ₃ C-COO	-CH ₂ O	O
NH ₂	H	H	CH ₃	CH ₃	(CH ₃) ₃ C-COO	-CH ₂ O	O
NH ₂	H	H	CH ₃	CH ₃	(CH ₂) ₃ CHCOO	-CH ₂ O	O

5

Example 19-[2-[Bis(pivaloyloxymethoxy)phosphoryl]methoxy]ethoxyadenine

- 10 To a suspension of 9-[2-(phosphonomethoxy)ethoxy]adenine (3.8mmol, 1.1g) in dimethylformamide (10ml) triethylamine (7.6mmol, 1.06ml) was added. The resulting mixture was stirred at room temperature for 5 min. and chloromethyl pivalate (15.21mmol, 2.19ml) was added. The reaction mixture was stirred at 60°C for 2h, then the solvent was evaporated under
- 15 reduced pressure and the residue dissolved in chloroform (200ml). The chloroform solution was washed with aqueous sodium hydrogen carbonate (2x40ml), water (40ml) and dried (MgSO₄). After evaporation of chloroform the residue was purified by column chromatography on silica gel (eluting with 4% ethanol in chloroform) to give the product as a
- 20 colourless oil (0.81g, 41%); $\delta_H[(CD_3)_2SO]$ 1.16 (18H, s, 2x(CH₃)₃C), 3.86 (2H, s, CH₂), 4.04 (2H, d, J 7.7, CH₂P), 4.51 (2H, m, 4.51, CH₂ON), 5.66 (4H, d, J 12.65, 2xCH₂OP), 7.38 (2H, br s, D₂O exchangeable, NH₂), 8.14 (1H, s), 8.33 (1H, s). (Found: C, 45.87; H, 6.29; N, 13.37; C₂₀H₃₂N₅O₉P.0.3 H₂O requires C, 45.89; H, 6.29; N, 13.34).

25

Example 29-[2-[Bis(1-pivaloyloxyethoxy)phosphoryl]methoxy]ethoxyadenine

- 30 To a suspension of 9-[2-(phosphonomethoxy)ethoxy]adenine (1.52mmol, 0.440g) in dimethylformamide (5ml), triethylamine (3.03mmol, 0.42ml) was added. The resulting mixture was stirred at room temperature for 5 min. and 1-chloroethyl pivalate (6.08mmol, 1.0ml) was added. The

reaction mixture was stirred at 80°C for 6h, then the solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (100ml). The dichloromethane solution was washed with aqueous sodium hydrogen carbonate (2x30ml), water (1x30ml) and dried (MgSO₄). After evaporation of dichloromethane the residue was purified by column chromatography on silica gel (eluting with 6% ethanol in chloroform) to give 25mg of the faster diastereomer, 50mg of the mixture of diastereomers and 75mg of the slower diastereomer, total yield 18%;

5 $\delta_H[(CD_3)_2SO]$ the faster diastereomer: 1.14 (18H, s, 2x(CH₃)₃C), 1.50 (6H, d, 2xCH₃), 3.82 (2H, m, CH₂), 3.95 (2H, d, J 7.42, CH₂P), 4.48 (2H, m, CH₂ON), 6.47 (2H, m, 2xCHOP), 7.37 (2H, br s, D₂O exchangeable, NH₂), 8.14 (1H, s), 8.31 (1H, s). (Found: C, 48.05; H, 6.40; N, 12.01; C₂₂H₃₆O₉N₅P requires C, 48.44; H, 6.65; N, 12.83). (Found: m/z (e.i.) 545.2251 C₂₂H₃₆N₉O₅P requires M⁺; 545.2251).

10 $\delta_H[(CD_3)_3SO]$ the slower diastereomer: 1.14 (9H, s, (CH₃)₃C), 1.16 (9H, s, (CH₃)₃C), 1.47 (6H, m, 2xCH₃), 3.85 (2H, m, CH₂), 3.97 (2H, m, CH₂P), 4.49 (2H, m, CH₂ON), 6.49 (2H, m, 2xCHOP), 7.38 (2H, br s, D₂O exchangeable, NH₂), 8.14 (1H, s), 8.33 (1H, s). (Found: C, 48.52; H, 6.66; N, 12.31; C₂₂H₃₆O₉N₅P requires C, 48.44; H, 6.65; N, 12.83). (Found: m/z (e.i.) 545.2251 C₂₂H₃₆O₉N₅P requires M⁺; 545.2251).

15
20

Example 3

9-[2-[Bis-(1-isobutyryloxyethoxy)phosphorylmethoxy]ethoxy]-adenine

25 To a suspension of 9-[2-(phosphonomethoxy)ethoxy]adenine (1.45mmol, 0.420g) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (5ml) triethylamine (3.42mmol, 0.48ml) was added. The mixture was stirred at room temperature for 10 min and 1-chloroethyl isobutyrate (0.5ml) was

30 added together with sodium iodide (1.67mmol, 0.250g). The resulting reaction mixture was stirred at 60°C for 5h after which further sodium iodide (1.67mmol, 0.250g) was added to it and stirring continued for a further 1h. The solid was filtered off, washed with dichloromethane, the filtrate concentrated to a small volume and precipitated into hexane at

35 0°C. The hexane solution was removed by decantation, the resulting oil dissolved in chloroform (150ml) washed with aqueous sodium hydrogen carbonate (30ml), water (30ml), dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica gel eluting with

5% ethanol in chloroform to afford the title compound as a mixture of diastereomers. (0.240g, 32%). $\delta_{\text{H}}[(\text{CD}_3)\text{SO}]$ 1.09 (12H, m, $\text{C}(\text{CH}_3)_2$, 1.49 (6H, m, CH_3C), 2.55 (2H, m, CHCO), 3.83 (2H, m, CH_2), 3.97 (2H, m, CH_2P), 4.48 (2H, m, CH_2O), 6.5 (2H, m, CH), 7.37 (2H, br s, D_2O exchangeable, NH_2), 8.14 (1H, s, H-2), 8.33 (1H, s, H-8). (Found: C, 44.13; H, 6.07; N, 12.55%. $\text{C}_{20}\text{H}_{32}\text{N}_5\text{O}_9\text{P} \cdot 0.25 \text{CHCl}_3$ requires C, 44.43; H, 5.94; N, 12.79%. (Found: M^+ , 517.1930 $\text{C}_{20}\text{H}_{32}\text{N}_5\text{O}_9\text{P}$ requires M, 517.1938).

Biological EvaluationProcedures

- 5 Compounds were administered as single doses of 0.2mmol/kg in 0.1ml of
1% carboxymethyl cellulose by oral gavage to female Balb/c mice weighing
20g. Food was withheld from the mice for 18 hours prior to the start of
the experiment. Blood was collected by cardiac puncture using
heparinised syringes 15, 60 and 180 mins after dosing. Equal volumes
10 (0.2ml) from 3 mice were pooled at each time point and 0.6ml of ice-cold
ethanol was added. Following chilling at -20°C and centrifugation, 0.5ml
of supernatant was dried under reduced pressure. The sample was then
reconstituted with 0.5ml of 0.4M NH₄OAc (pH 6.0) and analysed by
HPLC.

15

Results

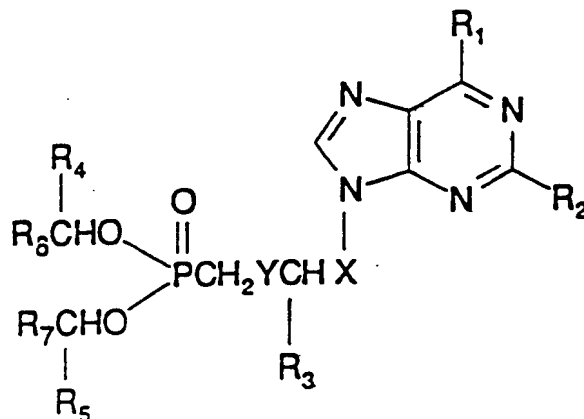
9-[2-(Phosphonomethoxy)ethoxy]adenine concn(mM)
in blood at time (min) after dosing

20

<u>Compound of Example No.</u>	<u>15</u>	<u>60</u>	<u>180</u>
1	14	10	1.1
2			
(mixture of diastereoisomers)	7	17	11
2			
(slower running diastereoisomer)	4	13	3
3			
(mixture of diastereoisomers)	11	4.5	1.4
Ex.1, EP-A-319228	<1	<1	<1

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is $-\text{CH}_2\text{O}$, $-\text{CH}_2$ or $-\text{CH}(\text{CH}_2\text{OR}_8)\text{O}$ where R_8 is hydrogen or acyl;

Y is O or S;

R_1 is hydroxy or amino;

R_2 is amino or hydrogen;

R_3 is hydrogen or, when X is CH_2O and Y is O, R_3 may be CH_2OR_9 where R_9 is hydrogen or acyl;

R_4 and R_5 are both hydrogen or the same C_{1-4} alkyl group; and

R_6 and R_7 are independently C_{2-7} alkanoyloxy or benzoyloxy wherein the phenyl moiety is optionally substituted.

2. A compound according to claim 1 wherein R_1 is hydroxy and R_2 is amino.

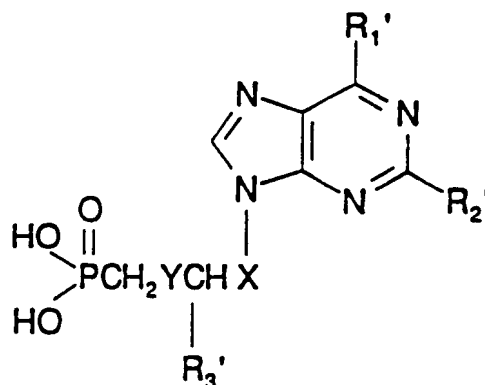
3. A compound according to claim 1 wherein R_1 is amino and R_2 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R_4 and R_5 are hydrogen or methyl.

5. A compound according to any one of claims 1 to 4 wherein R_6 and R_7 are pivaloyloxy or isobutyryloxy.

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6. A compound according to any one of claims 1 to 5 wherein X is $-\text{CH}_2\text{O}$ and R_3 is hydrogen.
7. A compound according to any one of claims 1 to 5 wherein X is $-\text{CH}_2\text{O}$ and R_3 is CH_2OR_9 as defined in claim 1.
8. A compound according to any one of claims 1 to 5 wherein X is $-\text{CH}_2(\text{CH}_2\text{OR}_8)\text{O}$ as defined in claim 1 and R_3 is hydrogen.
9. A compound according to any one of claims 1 to 5 wherein X is $-\text{CH}_2$ and R_3 is hydrogen.
10. A compound according to any one of claims 1 to 5 wherein X is $-\text{CH}_2$ and R_3 is CH_2OR_9 as defined in claim 1.
11. 9-[2-[Bis(pivaloyloxymethoxy)phosphorylmethoxyethoxy]adenine.
12. 9-[2-[Bis(1-pivaloyloxyethoxy)phosphorylmethoxy]ethoxy]adenine.
13. 9-[2-[Bis-(1-isobutyryloxyethoxy)phosphorylmethoxy]-ethoxy]adenine.
14. A compound according to claim 1, substantially as defined herein with reference to the examples.
15. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (II):



- 14 -

with R_6R_4CHQ and R_7R_5CHQ wherein Q is a leaving group and $R_1, R_2, R_3, R_4, R_5, R_6$ and R_7 are as defined in formula (I), and thereafter optionally forming a pharmaceutically acceptable salt thereof.

5 16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

17. A compound according to any one of claims 1 to 14 for use as an active therapeutic substance.

10

18. A compound according to any one of claims 1 to 14 for use in treating viral infections.

15

19. Use of a compound according to any one of claims 1 to 14 in the manufacture of a medicament for use in the treatment of viral infections.

20. A method of treatment of viral infections in mammals, which comprises the administration to mammal in need of such treatment, an effective amount of a compound according to any one of claims 1 to 14.

20

21. A compound, use or method according to any one of claims 18, 19 or 20 wherein the viral infection is a human immunodeficiency virus infection.

PCT/GB 91/02113

According to International Patent Classification (IPC) or to both National Classification and IPC
Int. Cl. 5 C 07 F 9/6561 A 61 K 31/675

Minimum Documentation Searched?

Classification Symbols

C 07 F 9/00 A 61 K 31/00

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Relevant to Claim No. 13

1,2-5,9
,10,15-
21

1-21:

1,2-5,9
,10,15-
21

"&" document member of the same patent family

15.04.92

 Danielle van der Haas

III. DOCUMENTS CONSIDERED TO BE RELEVANT

(CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0353955 (BEECHAM) 7 February 1990, see examples; claims (cited in the application) -----	1,2-5,7 ,15-21

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependant claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9102113
SA 53990

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/04/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0270885	15-06-88	AU-A- 8092587 JP-A- 63198683	19-05-88 17-08-88
EP-A- 0353955	07-02-90	AU-B- 614863 AU-A- 3913989 JP-A- 2088591 US-A- 5055458	12-09-91 08-02-90 28-03-90 08-10-91